Usmarapride (SUVN-D4010), a Selective 5-HT$_4$ Partial Agonist: An Update on the Clinical Development Program for the Treatment of Cognitive Disorders

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Introduction:

Cognitive disorders represent a heterogeneous group of conditions characterized by progressive impairment in memory, attention, executive function, and other higher-order cognitive abilities, ultimately affecting daily functioning and, in severe cases, leading to loss of independent living. There remains a substantial unmet need for safer and more effective therapies, particularly as the global burden of cognitive disorders is expected to rise significantly in the coming decades. In this context, 5-HT$_4$ receptors have emerged as a promising therapeutic target for improving cognitive deficits across disorders, with potential disease-modifying effects that may influence disease progression.

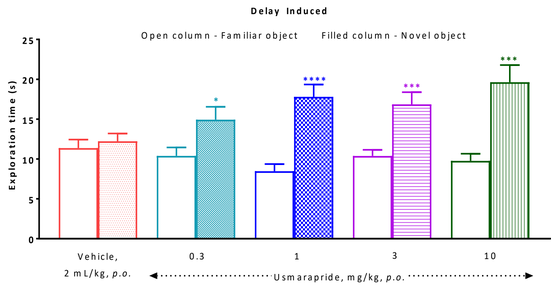
Usmarapride is a selective 5-HT$_4$ receptor partial agonist being developed for a potential treatment for cognitive disorders. The safety, tolerability, and pharmacokinetics of Usmarapride were evaluated in a single-center, multi-segment Phase-1 study following single and repeated administrations in healthy subjects.

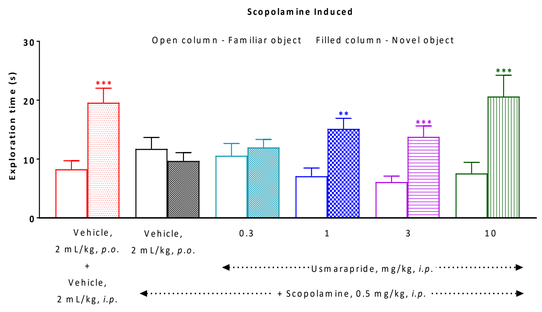
Objective:

To summarize the clinical development of Usmarapride for cognitive disorders.

Methods and Results:

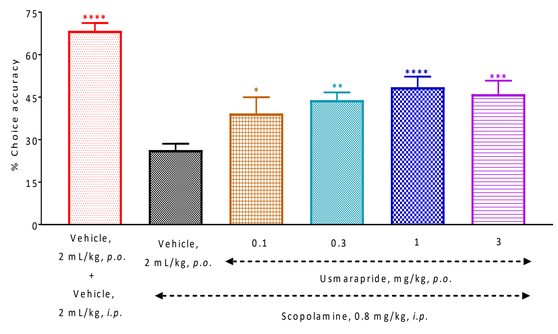
Episodic Memory (Object Recognition Task in Rats):



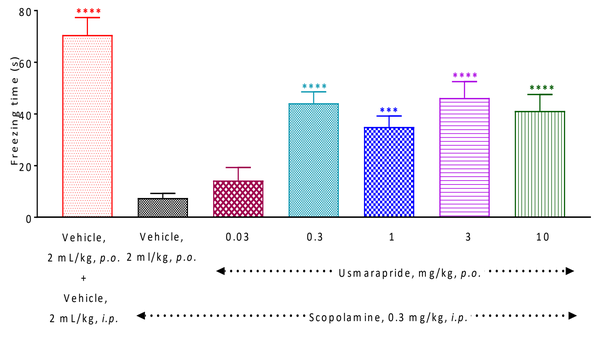


Data represents Mean ± SEM, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 Vs. familiar object.

Working Memory (Radial Arm Maze in Rats):

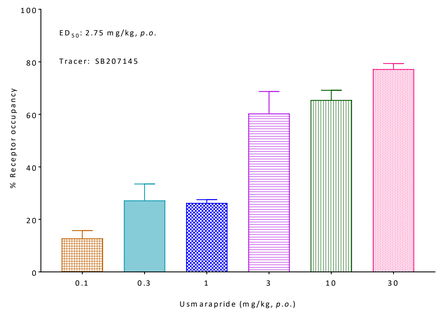


Emotional Memory (Fear Conditioning Task in Rats):

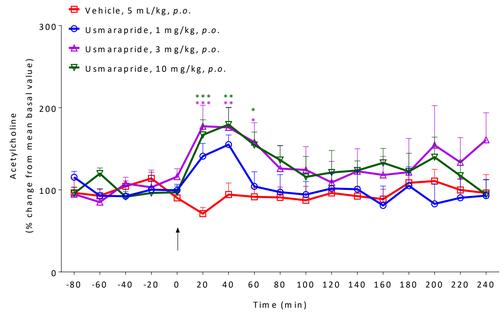


Data represents Mean ± SEM, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 Vs. scopolamine.

Receptor Occupancy in Rat Cortex:

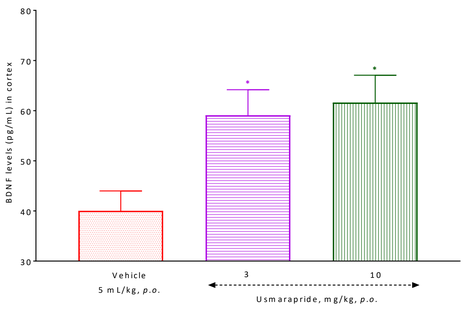


Acetylcholine Modulation in Rat Cortex:

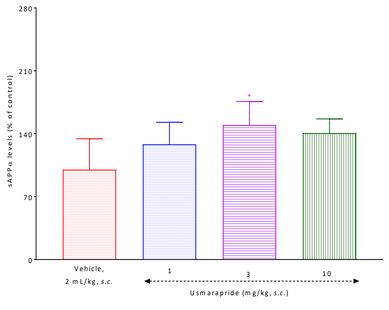


Data represents Mean ± SEM, *p<0.05, **p<0.01, ***p< 0.001 Vs. vehicle.

Brain Derived Neurotrophic Factor (BDNF) Levels in Rat Cortex:



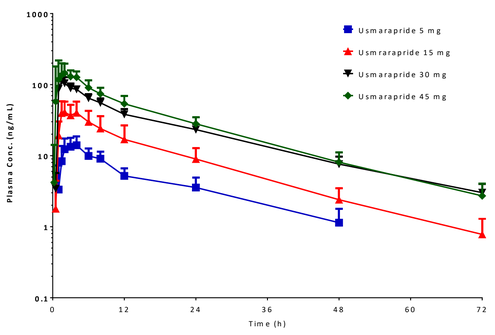
Cortical sAPPα Levels in Mice:



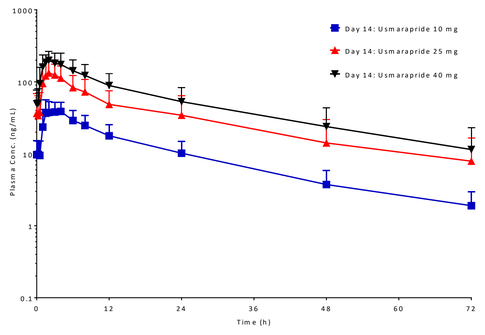
Data represents Mean ± SEM, *p<0.05 Vs. vehicle.

Human Pharmacokinetics:

Single Ascending Dose:



Multiple Ascending Dose:



Data represents Mean ± SD.

Conclusions:

- Usmarapride showed pro-cognitive effects across animal models assessing memory and modulated markers suggesting neuroprotective, and neurotrophic properties.
- Favorable pharmacokinetics for once a day dosing.
- Achieved projected efficacy concentrations at the tested dose levels.
- Usmarapride was safe and well tolerated with favorable pharmacokinetics in healthy subjects.

A Phase-2 proof-of-concept study in USA is currently being planned.